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Improving cardiovascular risk stratification through the derivation and validation of an elevated triglyceride-glucose index

Georgios Mavraganis MD[1] | Georgios Georgiopoulos MD[1,2] | Stavros Athanasopoulos MD[1] | Dimitrios Terentes-Printzios MD[3] | Georgios Zervas MD[1] | Christina Konstantaki MD[1] | Maria Eleni Koilakou MD[3] | Sofia-Panagiota Giannakopoulou MD[4] | Maria-Angeliki Dimopoulou MD[1] | Christina Chrysochoou MD[3] | Konstantinos Tsioufis MD[3] | Christos Pitsavos MD[3] | Evangelos Liberopoulos MD[5] | Konstantinos Stellos MD[6,7,8,9] | Charalambos Vlachopoulos MD[3] | Demosthenes Panagiotakos PhD[4] | Kimon Stamatelopoulos MD[1,10]

[1]Department of Clinical Therapeutics, Alexandra Hospital, National and Kapodistrian University of Athens Medical School, Athens, Greece

[2]Department of Physiology, School of Medicine, University of Patras, Patras, Greece

[3]First Department of Cardiology, Hippokration General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

[4]Department of Nutrition and Dietetics, School of Health Sciences and Education, Harokopio University, Athens, Greece

[5]First Department of Propaedeutic Internal Medicine, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, Athens, Greece

[6]Department of Cardiovascular Research, European Center for Angioscience (ECAS), Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

[7]Department of Medicine, University Medical Centre Mannheim, Heidelberg University, Mannheim, Germany

[8]German Centre for Cardiovascular Research (DZHK), Partner Site Heidelberg/Mannheim, Mannheim, Germany

[9]Helmholtz-Institute for Translational AngioCardioScience (HI-TAC) of the Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC) at the Heidelberg University, Heidelberg, Germany

[10]Biosciences Institute, Vascular Biology and Medicine Theme, Faculty of Medical Sciences, Newcastle University, Newcastle Upon Tyne, UK

Correspondence
Kimon Stamatelopoulos, MD, PhD, Department of Clinical Therapeutics, Alexandra Hospital, Medical School, National and Kapodistrian University of Athens, PO Box 11528, 80 Vas. Sofias Str, Athens, Greece.
Email: kstamatel@med.uoa.gr

Abstract

Background and Aims: Triglyceride-glucose (TyG) index, is an emerging prognostic biomarker in atherosclerotic cardiovascular disease (ASCVD). Validation of its clinical value and of clinically relevant prognostic cut-off, remains an unmet need to integrate TyG into primary prevention protocols.

Methods: To assess the clinical applicability of TyG, a composite of cardiovascular mortality, myocardial infarction, coronary revascularization or stroke was used as the primary endpoint in a general population cohort (ATTICA cohort, $n = 1677$,

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derivation cohort). Next, we derived an optimal prognostic TyG cut-off and externally validated it in a primary prevention cohort ($n = 1237$). To assess the clinical value of TyG, we analysed 1170 consecutively recruited patients from an ongoing registry aiming to stratify ASCVD risk (Athens Cardiometabolic Cohort) and assessed indices of subclinical arterial injury and progression of atherosclerosis. The TyG index was calculated by the formula: ln[fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2].

Results: TyG index was independently associated with increased CVD events in the derivation cohort (HR = 1.33, $p = 0.020$). The incremental value of a derived optimal cut-off of 8.46 over SCORE2 was confirmed in both derivation and validation cohorts [net reclassification index (NRI) = 0.668 and 0.469 respectively, Delta Harrell's C index = 0.054 and 0.044 respectively, $p < 0.05$ for all]. Elevated TyG index was associated with more diseased vascular beds (OR = 2.00, 95% CI 1.24–3.24), progression of subclinical carotid atherosclerosis (OR = 2.99, 95% CI 1.10–8.17) at follow-up and established ASCVD ($p < 0.05$ for all).

Conclusions: TyG is associated with increased prevalence and progression of subclinical and clinically overt ASCVD. In individuals assessed for primary prevention a TyG≥8.46 may serve as a risk enhancer.

KEYWORDS
cardiovascular disease, population study, insulin resistance, cohort study

1 | INTRODUCTION

Despite advances in atherosclerotic cardiovascular disease (ASCVD) prevention, residual cardiovascular (CV) risk remains a major challenge, even in optimally treated patients. Beyond traditional risk factors (TRFs), metabolic abnormalities—including altered body composition, steatotic liver disease, systemic low-grade inflammation, and kidney dysfunction—contribute to this risk, often clustering within the framework of metabolic syndrome (MetS), a well-established yet evolving cardiometabolic entity.[1] Metabolic abnormalities, recognized since the Framingham Study, were later linked to insulin resistance (IR) by Reaven.[2] Thereafter, alternative criteria emerged, leading to the 2023 reclassification of MetS as cardiovascular-kidney-metabolic (CKM) syndrome.[3]

Even with evolving criteria, MetS (or CKM) remains fundamentally driven by a dysmetabolic state that promotes vascular disease, diabetes, and obesity. Adipose dysfunction promotes IR, ectopic fat accumulation, and inflammation, disrupting lipid and glucose metabolism.[4] These derangements fuel vascular dysfunction, hypertension, and atherosclerosis, with dyslipidemia, oxidative stress, and immune activation amplifying plaque formation and CV risk.[1] While IR is central to this process, it is absent from standard MetS definitions due to the impracticality of gold-standard tests like the euglycemic insulin clamp (EHC).[5] Hyperinsulinemia alone is an unreliable marker, as it may reflect distinct metabolic phenotypes or disease stages, and waist circumference does not improve ASCVD risk stratification beyond traditional factors.[1] Identifying a feasible IR biomarker remains an unmet need for diagnosing subclinical IR and refining CKM risk prediction and prevention.[6–8]

The triglyceride-glucose (TyG) index has emerged as a promising, easy-to-calculate surrogate marker, directly reflecting the two key metabolic substrates of IR: glucose and triglycerides.[9,10] TyG correlates well with EHC-derived IR, with proposed cut-offs demonstrating high diagnostic accuracy.[9] Furthermore, TyG is an emerging prognostic biomarker in ASCVD. Studies have linked TyG to atherosclerosis,[11] arterial stiffness,[12] coronary artery calcification (CAC) progression,[13] and cardiovascular disease (CVD) incidence.[14] However, evidence on its predictive value for major adverse CV events remains limited,[15] with most studies conducted in Asian populations, raising concerns about external validity. Notably, these associations persist irrespective of diabetes status, with even stronger links observed in individuals with diabetes, reinforcing TyG's potential as a clinically viable cost-effective marker of IR and CV risk.[16]

We hypothesized that the TyG index as a simple, cost-effective surrogate of IR, has potential clinical applicability as a CVD biomarker in primary prevention. Therefore, we aimed to derive and externally validate the incremental prognostic value of an optimal cut-off value of TyG for CVD events over established guideline-proposed CVD risk scores, in a primary prevention population without established ASCVD. Furthermore, to assess the clinical value of the TyG index, we explored the associations of TyG with traits of increased cardiometabolic risk (subclinical and clinically over atherosclerosis, atherosclerosis progression) in a population with varying cardiometabolic risk.

2 | MATERIALS AND METHODS

2.1 | Study population

2.1.1 | Design

This is a retrospectively designed cohort study consisting of 3 independent prospective cohorts (ATTICA cohort, Athens Cardiometabolic cohort and Hippokration Hypertension cohort). Figure 1 depicts the flow chart of the study. The optimal derived cut-off of the TyG index for CVD events was derived in the ATTICA cohort and then externally validated in a pooled population of primary prevention patients from the Athens Cardiometabolic and Hippokration Hypertension cohorts together. Furthermore, in order to assess the clinical value of the TyG index, data from the Athens Cardiometabolic cohort were used and associations of the TyG index with angio- and cardiometabolic traits were investigated.

2.1.2 | ATTICA cohort (Derivation cohort: General population cohort)

The ATTICA study is a prospective, observational, population-based cohort investigation that was initiated in 2001 aiming to estimate the prevalence of common CV risk factors in the population.[17] All participants were free of ASCVD and other chronic diseases, according to the study protocol. From 3042 subjects recruited consecutively between 2001 and 2002, we identified and included in the study 1677 who (a) had complete information regarding baseline demographic data and consequently calculation of the TyG index was feasible, and (b) complete follow-up information for CVD events, without any loss to follow-up. Participants with partial follow-up were included in the analyses and censored at the time of their last available follow-up, whereas only those with no follow-up data were excluded from the cohort.

ATTICA study was approved by the Bioethics Committee of Athens Medical School. The study was carried out in accordance with the Declaration of Helsinki. All participants were informed about the study aims and procedures and provided written informed consent.

2.1.3 | Primary prevention cohort (Validation cohort)

This cohort results from pooling data from two primary prevention independent cohorts recruited for CVD risk factor management. Specific details for each cohort are described below.

2.1.4 | Athens Cardiometabolic cohort (Validation cohort)

This is a registry consisting of two substudies: one cross-sectional including all consecutively recruited patients (Substudy I) and one

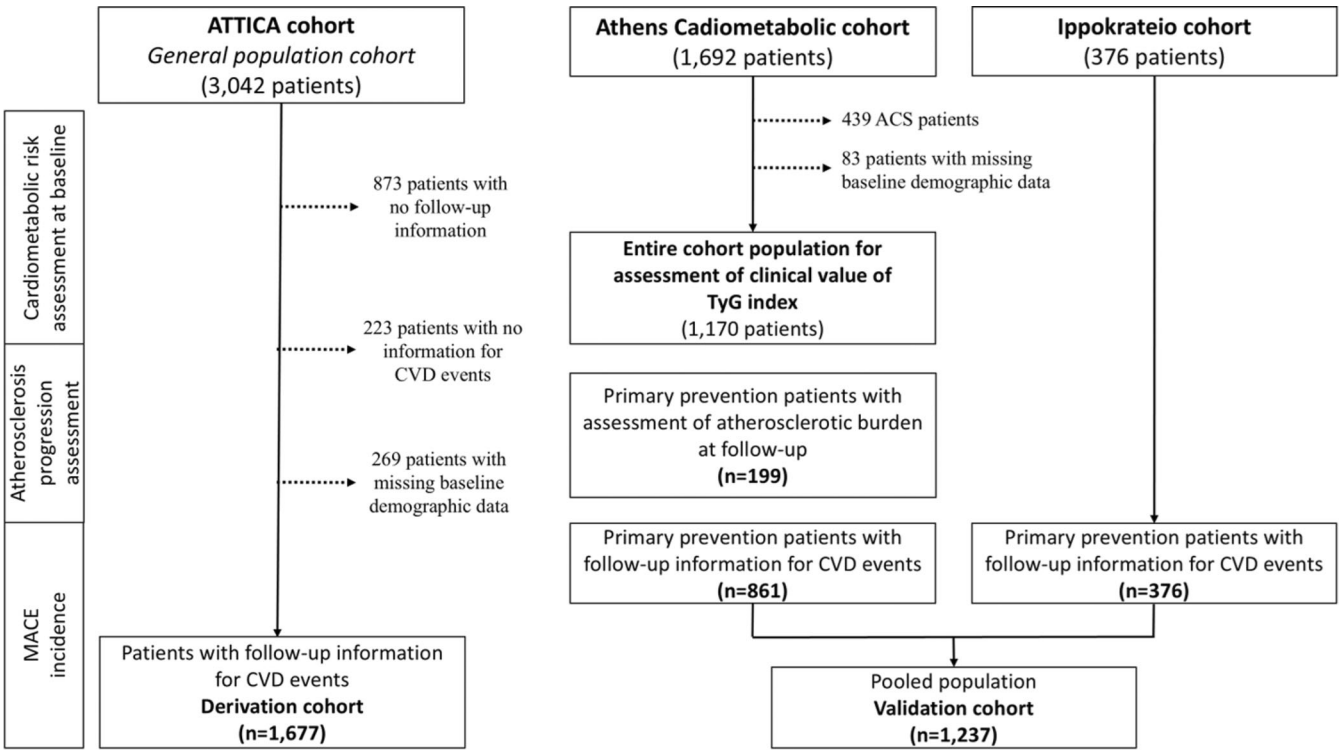

FIGURE 1 Flow chart of the study's populations. ACS, acute coronary syndrome; CVD, cardiovascular disease; MACE, major adverse cardiovascular events; TyG index, triglyceride-glucose index.

longitudinal part including consecutive patients who were followed for future events (Substudy II). This ongoing registry aims to stratify ASCVD risk in participants undergoing evaluation in primary or secondary ASCVD prevention settings. Recruitment is conducted at the Unit of Dyslipidemias and Atherosclerosis of the Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Alexandra Hospital, Athens, Greece, as previously described.[18] Our study design included participants from both substudies, as follows:

Substudy I. We performed a retrospectively designed post-hoc analysis on participants consecutively recruited between November 2015 and September 2019. Participants were included if they had no missing baseline demographic data as well as available triglyceride and glucose levels for TyG index calculation. These criteria resulted in a total population of $n = 1170$ patients.

Substudy II. Regarding the longitudinal part, from the 1170 patients in Substudy I, participants who consented to be followed for future events through telephone contact and through inspection of their medical records were included ($n = 1052$). Among them, $n = 25$ were lost to follow-up and $n = 1027$ were followed for future events, of whom 861 were primary prevention patients.

All participants provided written consent for participation in the registry. The current study was conducted according to the principles of the Declaration of Helsinki and the Local Ethics Committee of Alexandra General Hospital approved the study's protocol (13/26.11.2015). Further details are presented in the Data S1.

2.1.5 | Hippokration Hypertension cohort (Validation cohort)

Data from one large volume outpatient Hypertension clinic of the 1st Cardiology Department of National & Kapodistrian University of Athens, Hippokration Hospital, Athens, Greece was used for the analysis. Patients with both newly diagnosed and established hypertension were referred to outpatient clinics. Hypertensive status was confirmed by home and/or ambulatory blood pressure monitoring. Following blood pressure assessment, all patients underwent a comprehensive history and physical examination, along with routine laboratory tests as recommended by the European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension.[19] The current study was conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained from all participants, and ethical approval for accessing patient records was granted by the Local Ethics Committee of Hippokration Hospital.

2.1.6 | TyG index, cardiometabolic and vascular damage non-invasive indices at baseline

In the Athens Cardiometabolic cohort, at baseline, patients underwent blood sampling for metabolic profiling and peripheral vascular examination using established methods. Plasma glucose, triglycerides, high sensitivity C-reactive protein (hs-CRP), creatinine levels and lipid profile measurements were conducted in the fasting state by using standard analysers, as previously described.[20] TyG index was calculated as follows: ln[fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2].[20,21] Both triglycerides and glucose levels measurements were conducted in the fasting state to ensure correct measurement of TyG index; all blood measurements began at 08:00 h after 10 to 12 h overnight fast.[20] Regarding anthropometric measurements, BMI (kg/m^2), waist and hip circumference, as well as the waist-to-hip circumference ratio were estimated.

We employed high-resolution ultrasound imaging to assess subclinical atherosclerosis. We measured carotid intima media thickness (IMT), maximal wall thickness (maxWT), presence and number of carotid plaques, as previously described.[18]

Regarding measurement of adipose tissue thickness, participants underwent ultrasound examination at the level of the upper abdomen by an experienced physician in our laboratory.

Details about the measurement of these indices are provided in the Data S1.

2.2 | Calculation of ASCVD risk for prediction of major adverse events

In 3 cohorts who consisted of European (Greek) populations, we used the recommended by 2021 European Society of Cardiology (ESC) guidelines Systemic Coronary Risk Estimation 2 (SCORE2) and the Systemic Coronary Risk Estimation 2-Older Persons (SCORE2-OP) for persons aged <70 and ≥70 years respectively (country-specific calibrated version) to estimate the current 10-year fatal and non-fatal ASCVD risk for participants free of ASCVD.[1] The study population in each cohort was then divided into low-moderate, high and very high ASCVD risk categories based on 2021 ESC criteria. Accordingly, patients were categorized according to the risk category of SCORE2 (i.e. high and very high vs. low-moderate).

2.3 | Longitudinal follow-up for CVD events

The study endpoint comprised death from CV origin, non-fatal myocardial infarction (MI), coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) and stroke. In the ATTICA cohort, the follow-up of participants was primarily conducted at 5-year and 10-year intervals after the baseline examination, with a median follow-up of 10 years. Data collection involved interviews, contact through telephone calls and medical record reviews. For the purposes of the present analysis, the combined primary endpoint in the ATTICA cohort was the development of a fatal or non-fatal CVD event, defined according to the World Health Organization (WHO)–International Coding Diseases (ICD)-10 criteria.[17] Information on myocardial infarction, stroke and coronary revascularization procedures as distinct categories was not available.

In Athens Cardiometabolic cohort, in patients who consented to be followed for future events, follow-up evaluations were conducted annually either by site visit or by telephone contact if a site visit was not possible, as previously described.[18] End-of-study date for the current study for follow-up assessments (Substudy II) was set at the conclusion of September 2023. Median follow-up time was 4 years whereas the maximum follow-up was 7 years. Medical records were reviewed and evaluated by an independent clinician, blinded to the CV risk profile of participants, to adjudicate fatal events.

In Hippokration Hypertension cohort, participants were followed for a median of 12.5 years. Follow-up evaluations were conducted either by site visit or by telephone contact if a site visit was not possible.

In all cohorts, CV events were validated using hospital discharge diagnoses, death certificates, and thorough review of medical records.

3 | STATISTICAL METHODS

Normality of continuous variables was assessed using the Shapiro–Wilk test and visual inspection of histograms and P–P plots. Non-normally distributed variables were presented as medians (interquartile ranges) and compared using the Kruskal–Wallis test, while normally distributed variables were presented as means (standard deviation) and compared using one-way ANOVA. Restricted cubic splines (natural splines, RCS) with 3 knots across TyG distribution were applied to produce a dose–response curve and to flexibly model the potential nonlinear association of continuous TyG with the main endpoint, as previously described.[22] The 3 knots for RCS were fixed at the 10th, 50th and 90th percentiles of the TyG distribution. The number of knots was selected on the basis of improvement in log likelihood among regression models with 3- or 4-knot RCS. We used the Wald test to evaluate the significance of the nonlinear terms. Dose response curves were plotted as log hazard ratio (logHR) and continuous TyG. We visually inspected the RCS plots to identify the inflection point of the dose–response association of continuous TyG with the main endpoint, and we then formally derived the optimal cut-off point by implementing time-dependent ROC curve analysis.[23]

We used Kaplan–Meier curves and the log-rank test to illustrate survival differences between groups of patients according to the cut-off in TyG index. For longitudinal analysis of the association between TyG index and CVD events, univariable and multivariable Cox proportional hazards regression were employed. Multivariable models that evaluated the independent association of TyG index with CVD events were adjusted for age, sex, diabetes, hyperlipidemia, hypertension, smoking, alcohol intake and dietary pattern. The incremental prognostic value of the optimal cut-off point of TyG index in predicting CVD events over established guidelines-recommended risk score (i.e. SCORE2 or SCORE2-OP) was evaluated using delta Harrell's C index. To further evaluate incremental discrimination and reclassification, we applied the net reclassification index (NRI) according to established methodology.[24,25]

For assessment of the clinical value of TyG index, we employed regression analysis (i.e. linear regression and logistic regression) to evaluate the independent association between TyG index and subclinical atherosclerosis, arterial injury, hemodynamic and obesity markers as well as the extent of vascular beds involvement at baseline after adjusting for TRFs.

Baseline hazard rate was set at 5%. Type I error was prespecified at 0.05. Statistical analyses were conducted using SPSS 29 (IBM Corporation, Armonk, New York) and STATA v18.0 (STATACorp LLC). Significance was set at $p < 0.05$, and all tests were two-tailed. Further details about the statistical analysis are provided in the Data S1.

4 | RESULTS

4.1 | Demographic characteristics of the population according to TyG index by tertiles

Descriptive characteristics of the study population according to baseline TyG index by tertiles in the derivation cohort are shown in Table 1. Patients with TyG index at the highest tertile had a significantly higher prevalence of TRFs including hypertension, hyperlipidemia, smoking and diabetes compared with their counterparts at lower tertiles (Table 1). Similarly, patients with increased TyG index were older and exhibited significantly higher levels of hemodynamic markers including systolic blood pressure (SBP) and diastolic blood pressure (DBP) as well as increased low-density lipoprotein cholesterol and hs-CRP levels ($p < 0.001$ for all) (Table 1). Furthermore, TyG index was similar in the derivation [8.39 (7.99–8.78)] and validation cohort [8.45 (8.07–8.83)]. Baseline characteristics of the population in the derivation and validation cohort in parallel are demonstrated in Table S1.

4.2 | Optimal derived cut-off of TyG index and CVD events

In the ATTICA cohort, over a median follow-up of 10 years, 1677 patients were followed, and 269 of them (16.0%) suffered a CVD event, of which 81 were fatal. A nonlinear association was found between continuous TyG index and the risk of CVD events (Figure 2; p-value for nonlinear term = 0.004). Given the nonlinear association and aiming to identify a clinically relevant threshold, we derived a cut-off equal to 8.46. This cut point corresponded to the inflation point of the dose response curve (Figure 2). TyG index ≥8.46 was independently associated with increased risk for the combined endpoint of CVD events (HR = 1.47, $p = 0.015$) after adjusting for the model including TRFs (Table 2 and Figure 2).

In the ATTICA cohort, TyG index ≥8.46 provided incremental prognostic value for CVD events over SCORE2 (NRI = 0.668, events 33.1%, non-events 33.7%, 95% CI 0.537–0.798, $p < 0.001$ and delta Harrell's C index = 0.054, 95% CI 0.020–0.088, $p = 0.002$) (Table 2). This NRI indicates that, among 1677

TABLE 1 Baseline characteristics of the entire population and subgroups by TyG index tertiles in derivation cohort.

ATTICA cohort (General population cohort)					
Variable	All (6.72–11.57) (*n* = 1677)	1st tertile (6.72–8.12) (*n* = 559)	2nd tertile (8.13–8.64) (*n* = 559)	3rd tertile (8.64–11.57) (*n* = 559)	*p* value
Cardiometabolic risk factors					
Age (years)	43.9 (13.6)	37.2 (12.0)	45.3 (12.9)	49.0 (13.1)	<0.001
Sex (male) (*n*, %)	825 (49.2)	175 (31.3)	263 (47.0)	387 (69.2)	<0.001
BMI (kg/m^2)	26.3 (4.6)	24.1 (4.0)	26.5 (4.4)	28.1 (4.4)	<0.001
Smoking (*n*, %)	699 (41.7)	209 (37.4)	233 (41.7)	257 (46.0)	0.014
Hypertension (*n*, %)	484 (28.9)	95 (17.0)	159 (28.4)	230 (41.1)	<0.001
Hyperlipidemia (*n*, %)	726 (43.3)	97 (17.4)	249 (44.5)	380 (67.0)	<0.001
Diabetes mellitus (*n*, %)	102 (6.1)	2 (0.4)	14 (2.5)	86 (15.4)	<0.001
Alcohol intake (≥moderate) (*n*, %)	866 (51.6)	305 (54.6)	276 (49.4)	285 (51.0)	0.028
MD (adherence) (*n*, %)					
Low	181 (10.8)	38 (6.8)	62 (11.1)	81 (14.5)	<0.001
Moderate	1438 (85.7)	491 (87.8)	481 (86.0)	466 (83.4)	
High	58 (3.5)	30 (5.4)	16 (2.9)	12 (2.1)	
SES (high) (*n*, %)	350 (35.2)	131 (35.5)	117 (37.4)	102 (32.7)	0.466
SBP (mmHg)	122.2 (18.3)	114.8 (16.1)	123.2 (17.2)	128.5 (18.8)	<0.001
DBP (mmHg)	78.9 (11.7)	74.1 (11.4)	79.9 (11.0)	82.4 (11.3)	<0.001
Fasting glucose (mg/dl)	92.3 (23.0)	83.7 (11.3)	90.0 (11.9)	102.8 (33.2)	<0.001
Total cholesterol (mg/dl)	194.2 (41.4)	168.5 (32.3)	196.9 (37.3)	215.9 (39.6)	<0.001
HDL-C (mg/dl)	48.3 (14.1)	53.6 (14.8)	48.6 (12.4)	43.0 (13.0)	<0.001
LDL-C (mg/dl)	122.4 (37.7)	104.1 (30.0)	128.3 (36.2)	133.7 (39.6)	<0.001
Triglycerides (mg/dl)*	98 (68–145)	58 (49–69)	98 (85–110)	169 (142–217)	<0.001
hs-CRP (mg/L)*	1.1 (0.5–2.4)	0.6 (0.3–1.6)	1.2 (0.5–2.5)	1.5 (0.7–3.2)	<0.001
GFR (ml/min/1.73 m^2)	96.0 (29.5)	93.7 (27.7)	95.5 (28.8)	98.8 (31.7)	0.015

Note: Continuous variables are presented as mean (SD) or median (interquartile ranges) and nominal as count (absolute percentages). Asterisk denotes non-normally distributed variables which are presented as median and interquartile ranges. Normally distributed variables were compared using one-way ANOVA, and non-normally distributed variables using the Kruskal–Wallis test (denoted by asterisk). Statistical significance was set at the level of P-value <0.05. SES data were available in 994 patients in total. *p*-value is derived by one way analysis of variance (ANOVA) for continuous variables and the chi-squared test for categorical ones.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MD, mediterranean diet; SBP, systolic blood pressure; SES, socioeconomic status; TyG index, triglyceride-glucose index.

individuals (269 CVD events), approximately 563 participants were more appropriately reclassified when TyG was added to SCORE2, including 89 correctly reclassified events and 474 correctly reclassified non-events. Similarly, in the pooled study population of Athens Cardiometabolic and Hippokration Hypertension cohorts consisting of primary prevention patients, after a median follow-up of 5 years, 1237 patients were followed. From those, 63 patients (5.1%) experienced a CVD event (31 CV deaths, 22 MIs and 10 revascularizations). In these patients, TyG index ≥8.46 retained its prognostic superiority over the SCORE2 for CVD events (NRI = 0.469, events 42.9%, non-events 4% and delta Harrell's C index = 0.044, $p < 0.05$ for both) (Table 2). This NRI corresponded to 74 correctly reclassified individuals, including 27 events and 47 non-events. In patients with established ASCVD, TyG was not independently associated with increased risk for the primary endpoint (HR = 1.10, 95% CI 0.72–1.69, $p = 0.651$) (Table S2).

4.3 | Associations of TyG index with subclinical atherosclerosis, extent of vascular beds involvement, hemodynamic and cardiometabolic markers

Descriptive characteristics of the Athens Cardiometabolic cohort according to baseline TyG index by tertiles are shown in Table S3. After multivariable analysis, increased TyG index was independently associated with subclinical atherosclerotic burden and arterial stiffness markers (Table S4). In detail, increased TyG index was independently associated with the number of diseased vascular beds ≥3 (OR = 2.00, 95% CI 1.24–3.24),

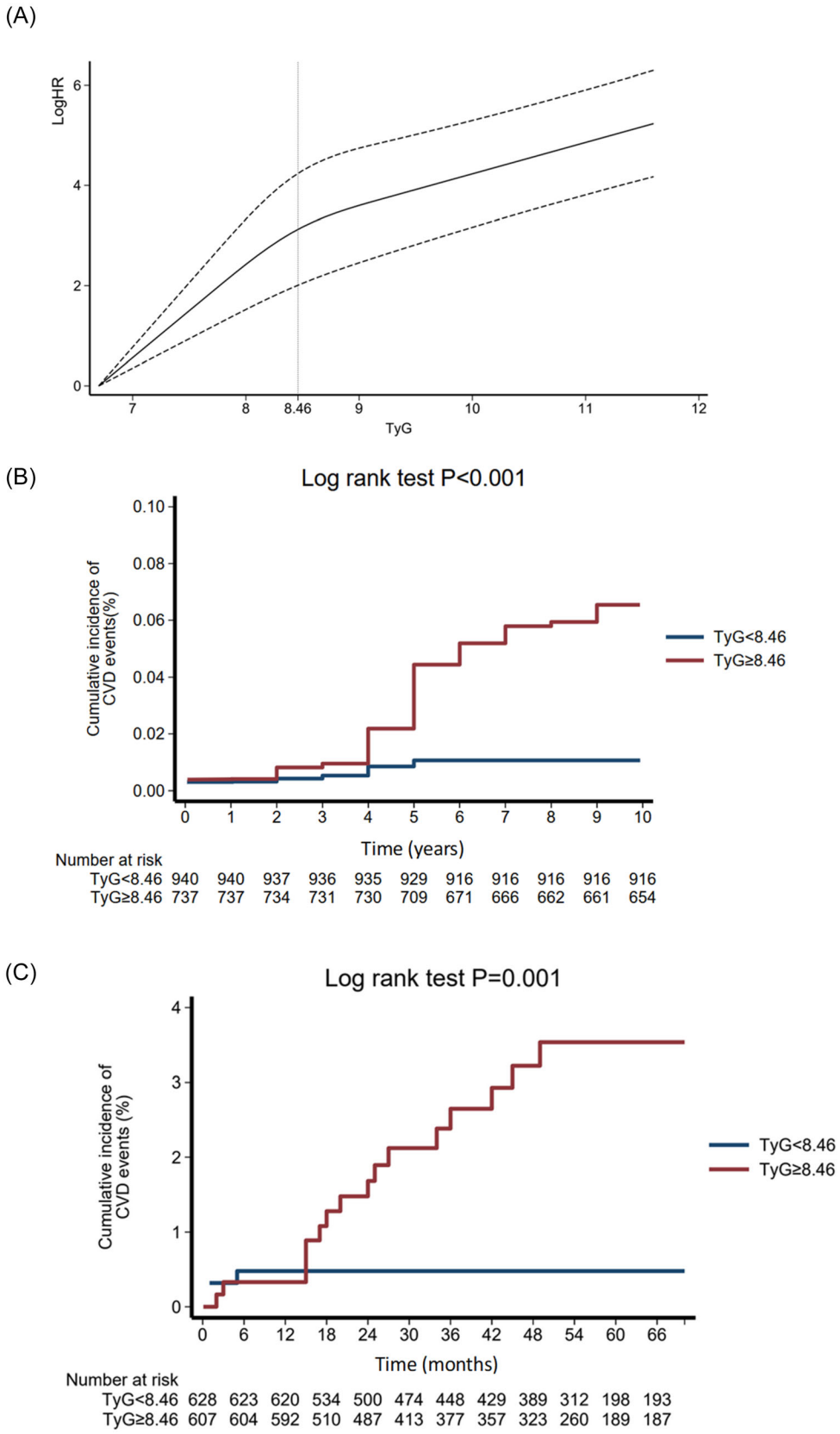

FIGURE 2 A. Smoothed restricted cubic spline plots of the HR for the composite endpoint of CV death, MI, revascularization and/or stroke versus the baseline levels of TyG index in the ATTICA cohort. Nelson Aalen curves for the cumulative incidence of the composite endpoint of CV death and/or MI and/or revascularization and/or stroke according to the cut-off of TyG index (8.46) in (B) ATTICA cohort and (C) validation cohort. Three knots were fixed at the 10th, 50th and 90th percentile of TyG index distribution. The upper- and lower-most dashed curves represent the 95% CI about the predicted HRs (middle solid line). The horizontal tight-dot line indicates zero effect (HR = 1) while the vertical tight-dot line shows the cut-off point of 8.46 in TyG index. Nelson Aalen curves for the cumulative incidence of the composite CVD according to the cut-off of TyG index (8.46) in ATTICA cohort demonstrated that 188 out of 737 patients (25.5%) with TyG index ≥8.46 suffered a CVD event vs. 81 out of 940 patients (8.6%) with TyG index <8.46 who suffered a CVD event. Similarly, in the pooled study population of Athens Cardiometabolic and Hippokration Hypertension cohort, 45 out of 608 patients (7.4%) with TyG index ≥8.46 suffered a CVD event vs. 18 out of 629 patients (2.9%) with TyG index <8.46 who suffered a CVD event. The Nelson-Aalen plots depict the cumulative hazard rate function from survival data across a time period, separately for each group of interest (i.e., patients with TyG index ≥8.46 vs. patients with TyG index <8.46). The risk table beneath these plots shows the number of patients at risk of experiencing the event for each time. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; TyG, triglyceride-glucose index.

maxWT≥2 mm (OR = 1.57, 95% CI 1.16–2.14), PWV > 10 m/s (OR = 1.51, 95% CI 1.10–2.06) as well as hs-CRP >2 mg/dL (OR = 1.32, 95% CI 1.02–1.69), even after additional adjustment for the presence of CAD ($p < 0.05$ for all) (Table S4 and Figure 3).

In the same population, increased TyG index expression was independently associated with hemodynamic markers including DBP (mean increase = 2.07 mmHg, 95% CI 0.92–3.22) and aortic DBP (mean increase = 2.63 mmHg, 95% CI 1.33–3.92) ($p < 0.001$ for both) (Table S5).

TABLE 2 Cox regression and additive reclassification value of TyG index for predicting adverse CVD events.

ATTICA cohort-General population cohort ($N = 1677$ patients)				
CV death and/or MI and/or revascularization and/or stroke				
Regression				
Variable		HR (95% CI)		*p* value
TyG index + Cardiometabolic risk factors				
TyG index (continuous) (Univariable)		2.47 (2.11, 2.89)		<0.001
TyG index + Age		1.65 (1.38, 1.98)		<0.001
TyG index + Sex (male)		2.39 (2.03, 2.82)		<0.001
TyG index + Diabetes		1.92 (1.60, 2.31)		<0.001
TyG index + Smoking		2.54 (2.17, 2.97)		<0.001
TyG index + Hyperlipidemia		2.30 (1.94, 2.73)		<0.001
TyG index + Hypertension		2.20 (1.86, 2.60)		<0.001
TyG index + BMI		2.35 (1.90, 2.73)		<0.001
TyG index + hs-CRP		2.41 (2.04, 2.86)		<0.001
TyG index + GFR		2.54 (2.17, 2.97)		<0.001
TyG index (Multivariable[a])		1.31 (1.04, 1.65)		0.023
TyG index (Multivariable[b])		1.33 (1.05, 1.70)		0.020
Optimal derived cut-off value of TyG index + Cardiometabolic risk factors				
TyG index ≥8.46 (Univariable)		3.18 (2.45, 4.12)		<0.001
TyG index ≥8.46 + Age		1.88 (1.44, 2.45)		<0.001
TyG index ≥8.46 + Sex (male)		2.97 (2.27, 3.89)		<0.001
TyG index ≥8.46 + Diabetes		2.56 (1.94, 3.36)		<0.001
TyG index ≥8.46 + Smoking		3.25 (2.51, 4.22)		<0.001
TyG index ≥8.46 + Hyperlipidemia		2.76 (2.09, 3.64)		<0.001
TyG index ≥8.46 + Hypertension		2.72 (2.07, 3.58)		<0.001
TyG index ≥8.46 + BMI		2.81 (2.14, 3.71)		<0.001
TyG index ≥8.46+ hs-CRP		3.01 (2.29, 3.96)		<0.001
TyG index ≥8.46 + GFR		3.53 (2.71, 4.61)		<0.001
TyG index ≥8.46 (Multivariable[a])		1.50 (1.11, 2.02)		0.008
TyG index ≥8.46 (Multivariable[b])		1.47 (1.08, 2.01)		0.015
Reclassification				
New predictor vs Baseline predictor	NRI (95% CI)	*p*-value	Delta Harrell's C index (95% CI)	*p*-value
ATTICA cohort-General population cohort				
TyG index ≥8.46 and SCORE2 vs. SCORE2	0.668 (0.537, 0.798)	<0.001	0.054 (0.020, 0.088)	0.002
Athens Cardiometabolic & Hippokration Hypertension cohorts—Primary prevention				
TyG index ≥8.46 and SCORE2 vs. SCORE2	0.469 (0.215, 0.722)	<0.001	0.044 (0.002, 0.085)	0.038

Note: Statistical significance was set at the level of *p*-value <0.05.

Abbreviations: BMI, body mass index; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; GFR, glomerular filtration rate; HR, hazard ratio; hs-CRP, high sensitivity C-reactive protein; MI, myocardial infarction; NRI, net reclassification index; SCORE2, Systematic Coronary Risk Evaluation 2; TyG index, triglyceride-glucose index.

[a]Adjusted for age, sex, smoking, hypertension, hyperlipidemia and diabetes mellitus; TyG included as an independent variable.

[b]Adjusted for age, sex, smoking, hypertension, hyperlipidemia, diabetes mellitus, alcohol intake and diet; TyG included as an independent variable.

Furthermore, after multivariable analysis, patients with increased TyG index had more than a 2-fold increased associated risk for obesity defined as BMI > 30 kg/m^2 (OR = 2.06, 95% CI 1.59–2.68) and more than a 2.8-fold increased associated risk for abdominal obesity (OR = 2.88, 95% CI 1.91–4.35) ($p < 0.001$ for both). Similarly, increased TyG index was independently associated with increased values of ultrasound lipid layers including preperitoneal fat tissue (mean increase = 0.23) and subcutaneous fat tissue (mean increase = 0.14) ($p < 0.05$ for both) (Table S6 and Figure 3).

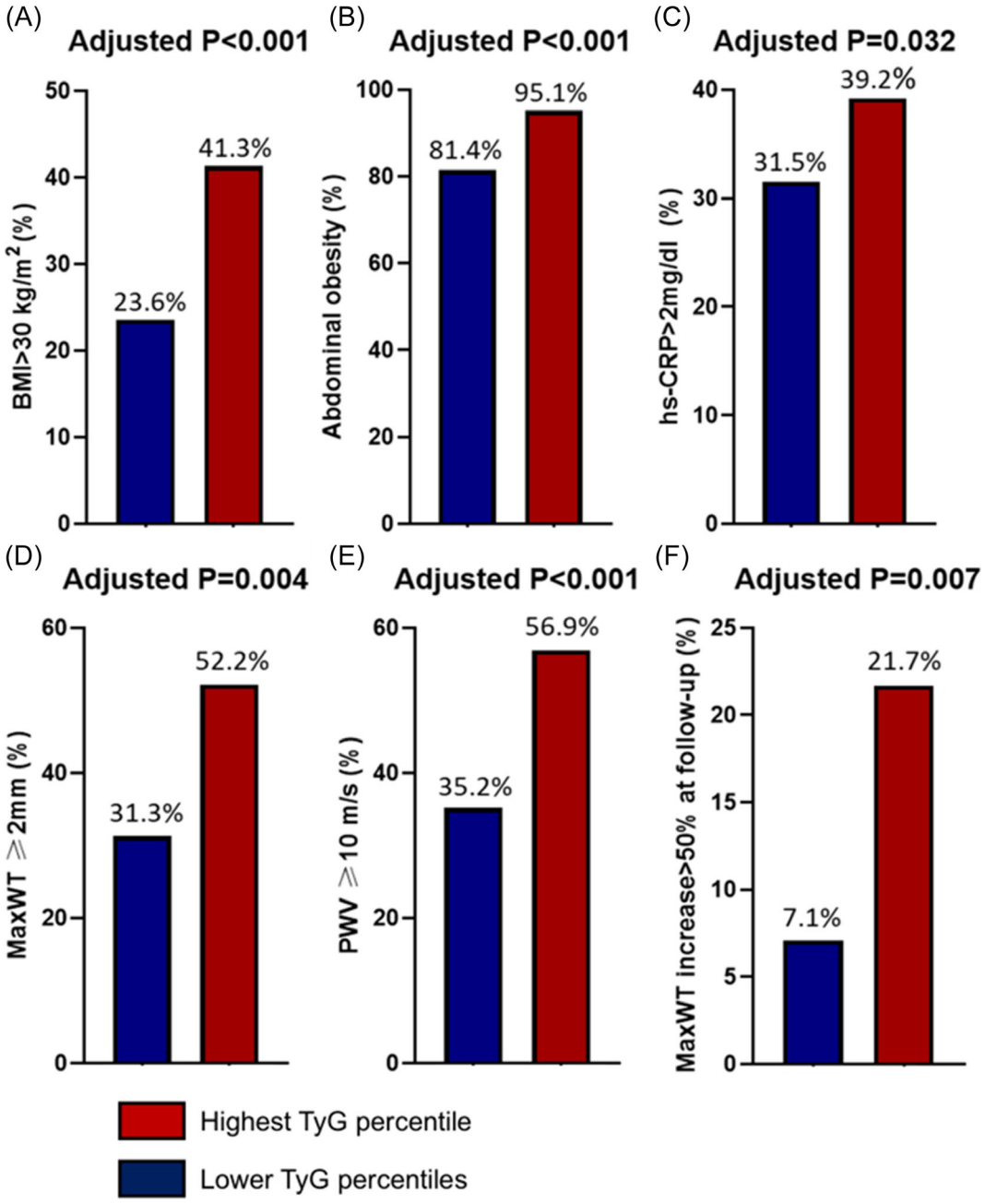

FIGURE 3 Association of TyG index with cardiometabolic traits. (A) BMI >30 kg/m^2, (B) Abdominal obesity, (C) hs-CRP >2 mg/dL, (D) MaxWT ≥2 mm, (E) PWV ≥ 10 m/s, (F) MaxWT increase ≥50% at follow-up. Red bars correspond to highest tertile of TyG whereas blue bars correspond to lower tertiles of TyG except for maxWT increase (F) where highest quartile vs. lower quartiles is shown. P-value is derived from multivariable logistic regression analysis. Abbreviations: TyG index, triglyceride-glucose index; BMI, body mass index; hs-CRP, high sensitivity C-reactive protein; MaxWT, maximal wall thickness; PWV, pulse wave velocity.

4.4 | Associations of TyG index with progression of atherosclerosis

In non-CAD patients, increased TyG index at baseline was associated with accelerated burden of atheromatosis (i.e., more than two new arterial plaques compared to baseline ultrasound evaluation) in the carotid arteries (OR = 2.99, 95% CI 1.10–8.17, $p = 0.033$) or in carotid/femoral arteries (OR = 2.60, 95% CI 1.10–6.14, $p = 0.030$) or with >50% increase in maxWT at follow-up compared with baseline (OR = 4.37, 95% CI 1.50–12.69, $p = 0.007$) after adjustment for the core model including TRFs (Table S7 and Figure 3).

Moreover, patients without overt CAD and with TyG index at the highest quartile had significantly increased maxWT at follow-up in comparison with baseline values (2.00 mm vs. 1.76 mm, $p < 0.001$, delta percentage + 13.6%), compared with patients at lower TyG quartiles (1.57 mm vs. 1.46 mm, $p < 0.001$, delta percentage + 7.5%).

Associations of TyG with subclinical atherosclerotic burden between baseline and follow-up in non-CAD patients are demonstrated in Table S7.

5 | DISCUSSION

The current study provides new evidence by demonstrating the applicability of TyG as a novel prognostic risk enhancer in primary prevention settings. This was shown by deriving a clinically relevant prognostic cut-off and validating it in a pooled population of two independent cohorts. In contrast, we could not establish the independent prognostic value of this marker in the secondary prevention subgroup. TyG was associated with both the presence and progression of ASCVD, mechanistically supporting our main findings.

To explore the clinical applicability of TyG, we evaluated the prognostic value of TyG across CV risk strata. In moderate-to-high-risk individuals, TyG significantly improved risk prediction. However, in very high-risk CAD patients, TyG was not associated with CVD events, suggesting diminished prognostic utility. External validation in a pooled population of primary prevention patients from two independent cohorts with low-to-moderate risk confirmed these findings. Specifically, we identified a TyG threshold of 8.46 as an independent predictor of CVD events in primary prevention, with no significant association in individuals with established CVD, consistent with previous evidence in chronic coronary disease populations.[26] Importantly, TyG provided incremental prognostic value over ESC guidelines recommended SCORE2 or SCORE2-OP.[1] While previous studies identified 4.68 as optimal for detecting the presence of IR assessed by EHC,[9] our results suggest that higher TyG cut-offs reflecting more severe downstream effects of IR, may capture more accurately CVD risk.[27] Additionally, our study population, comprising individuals with at least one cardiometabolic risk factor, had TyG values largely above the IR threshold. This aligns with the notion that IR precedes clinical manifestations by years.[4,28] Previous studies in hypertensive and diabetic populations reported slightly higher thresholds for CVD risk.[29,30] Our results, suggest a threshold of 8.46 as clinically meaningful for predicting CVD events in individuals without clinically overt ASCVD, which was confirmed and externally validated supporting the wide applicability of TyG in primary prevention as a risk enhancer in Caucasian individuals. Notably, this prognostic value is derived from hard CV endpoints including CV death, MI, revascularization, and stroke. Its associations with markers of subclinical arterial damage serve as supportive findings that provide mechanistic insight. This is important given that one of the criteria for the validation of a prognostic biomarker, is to create mechanistic evidence supporting its clinical value.[31]

The above has direct clinical implications, as better risk stratification in primary prevention is crucial to addressing residual CV risk. The clinical applicability of metabolic biomarkers—such as TyG—requires prognostic cut-off validation, as current ASCVD risk assessment relies on risk scores and non-quantified risk enhancers.[1] Derived from routine laboratory tests, the TyG index can be seamlessly incorporated into electronic health records or risk calculators, offering a practical and cost-effective biomarker for both individual CV risk assessment and large-scale population screening. Refining risk classification is particularly relevant with emerging obesity-targeting therapies, such as incretin-based treatments,[32] alongside redefining obesity to include CKM derangement,[33] to better identify high-risk individuals who would benefit most from intensified prevention. Given that TyG reflects both IR and adverse adiposity,[34] it serves as a widely applicable determinant of high-risk individuals in primary prevention.[35]

While IR is linked to dyslipidemia, glucose dysmetabolism, and CKM burden,[36] TyG's predictive value diminishes in overt ASCVD, suggesting a shift in risk drivers after CVD onset.[4] Factors such as hyperglycemia, endothelial dysfunction, atherogenic dyslipidemia, inflammation, fibrosis, and vascular remodelling become more prominent. Additionally, the widespread use of treatments targeting multiple risk factors introduces a treatment bias, further reducing TyG's independent predictive value. This is exemplified by the superior CV benefits of sodium/glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists, which act through mechanisms beyond insulin sensitization and outperform traditional insulin-sensitizing agents in established CVD, not limited to diabetes.[37] These therapies have highlighted renal dysfunction, obesity burden, and hemodynamic strain as key contributors, reinforcing a shift in pathophysiology where insulin resistance plays a lesser role in overall risk stratification.

To assess the clinical value of the TyG index, we explored the associations of TyG with cardiometabolic traits, atherosclerosis and arterial injury. Elevated TyG was linked to a higher prevalence of CAD and subclinical atherosclerosis, as indicated by carotid plaques, mean IMT, and maxWT. Our findings align with evidence showing TyG confers a 1.5-fold increased risk for arterial stiffness and CAC in Asian populations[12] and nearly a 2-fold increased risk for CAD.[26] Building on our prior work in lean postmenopausal women,[38] this study extends these findings to a broader Caucasian population with diverse cardiometabolic risk.

Given our findings, we examined whether TyG predicts atherosclerosis progression. Individuals in the highest TyG tertile had over twice an associated risk of developing additional carotid and/or femoral plaques and nearly a 4.5-fold associated increased risk of >50% maxWT progression. This association remained significant when TyG was combined with individual CKM syndrome components and was particularly pronounced in those with advanced age, diabetes, abdominal adiposity, and renal dysfunction/hyperfiltration. Our findings align with prior evidence linking elevated TyG to a 1.8-fold increased risk of CAC progression in Koreans.[13] Notably, TyG was the only marker predicting a > 50% increase in maxWT, a recognized predictor of future CVD events, even beyond traditional risk scores.[18] Taken together, these findings align with previous results and suggest potential underlying pathophysiological mechanisms that provide further mechanistic insight into the clinical relevance of TyG index.

Several limitations should be acknowledged. First, the associations between TyG and cardiometabolic traits do not allow conclusions for causal inference; however, they provide potential

mechanistic insight into the clinical relevance of the TyG index. Secondly, our results should be carefully interpreted in different ethnic settings. Prior research on TyG and mortality has been inconsistent, with a meta-analysis of four studies from Asia leading to no association, though with very low certainty,[15] and a population-based study from the U.S. suggesting a U-shaped association.[39] Expanding on this, a large multinational study across various continents demonstrated an association between TyG and all-cause mortality or CV events, with the strength of the effect varying based on country income.[40] Given the racial and socioeconomic heterogeneity of these populations, our findings, suggest that vulnerability to IR is multifactorial and cannot be fully explained by biological factors alone. It should be acknowledged that all three cohorts included in our analysis represent primary prevention populations from the Athens area, encompassing both community-based and outpatient settings. While differences in recruitment and participant characteristics exist between the cohorts, the derived prognostic cut-off value for TyG performed well in both cohorts. Therefore, these variations enhance the external validity and generalizability of our findings across a broad spectrum of individuals at risk for CVD but without established CVD. Finally, we did not directly assess short-term variability of TyG. Albeit this may introduce measurement error, prior studies show it is modest and not independently predictive of CVD risk, though residual variation may affect classification near cut-off values.[41,42]

In a population with a wide range of cardiometabolic risk, TyG was associated with increased prevalence and progression of subclinical arterial injury and an adverse metabolic profile. In individuals assessed for primary prevention, a TyG≥8.46 conferred incremental value over a well-established guidelines-recommended score, supporting its clinical applicability in this setting. These findings suggest that the addition of TyG ≥8.46 to established risk models may improve CVD risk prediction beyond traditional factors. Further research is warranted to validate a modified risk score calculator integrating the TyG index as a dichotomous variable in diverse populations.

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The authors have no conflicting interests to declare in regard to this manuscript.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

ORCID

Stavros Athanasopoulos https://orcid.org/0000-0003-0421-0227
Konstantinos Stellos https://orcid.org/0000-0002-0194-0825
Demosthenes Panagiotakos https://orcid.org/0000-0001-8583-153X
Kimon Stamatelopoulos https://orcid.org/0000-0001-6444-8734

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SUPPORTING INFORMATION

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